DISCOVERY OF UREA STIBAMINE BY U. N. BRAHMACHARI : A REAPPRAISAL

SYAMAL ROY*

Upendranath Brahmachari's birth in 1875 (June 7) coincided with the tail end of an epidemic of what was most certainly visceral leishmaniasis or kala-azar. The event was perhaps more than a mere coincidene for it seems to have shaped his future life dedicated to the discovery of a cure for this scourge. His educational upbringing was helpful in attaining this achievement. He had a successful career as a student in the Calcutta Medical College where from he obtained the degree of Doctor of Medicine (M.D.) in 1902. He was also interested in Chemistry and passed the M.Sc. Examination in Chemistry from the University of Calcutta. Later he obtained the degree of Ph.D. from the University in Physiology in 1909 with research work on "Haemolysis". Brahmachari entered the Provincial Medical Services in 1898, acted as a teacher in Medicine in several medical institutions and subsequently became Professor of Tropical Medicine at Carmichael Medical College, Calcutta.

Around this time, at the turn of the century, Charles Donovan and William Leishman had independently reported about the existence of a new parasite as the causative agent of kala-azar. To avoid controversy over priorities that could have created unpleasantness Ronald Ross quickly and neatly christened the new genus *Leishmania* and the species *donovani*. One *Leishmania donovani* had been identified as the causative agent of kala-azar, news spread and from many areas it was reported that this disease was in epidemic form. It was called kala-azar or black fever because the skin turned dark in chronic cases. This is accompanied by enlargement of spleen, liver, a gradual down-hill course with progressive emaciation, anaemia, leucopenia leading to marked cachexia and haemorrhage in different parts of the body.

Sir Leonard Rogers, F.R.S., was the first in India to use an antimony compound in the form of tartar emetic for the treatment of Kala-azar in Assam in 1919. Because of the toxicity of tartar emetic it was soon replaced by sodium antimony tartrate which had proved to be a safe drug and gave much more satisfactory results. But the treatment had the disadvantage of being long and tedious, and therefore difficult to enforce. Patients who had been completely incapacitated by the disease improved so much after a few injections that they discontinued treatment altogether or continued irregularly. These made it exceedingly difficult to effect complete cure. It was felt that these difficulties could be overcome using a drug which was at least as efficacious as sodium antimony tartrate but took a much shorter time to effect cure.

The nucleus of experimental chemotherapy was meanwhile established by Paul Ehrlich who had developed the organic arsenical Atoxyl for treatment of African sleeping sickness. Greatly inspired by this work, young Brahmachari set off on a search for organic pentavalent antimony derivatives that would fulfil Ehrlich's criteria for a Therapia sterilians magna, viz. a compound with minimum "organotropism" and maximum "parasitotropism". With his imaginative genius he prepared several hundred compounds and tested them in mice and, in selected instances, in man. Within a short time Brahmachari struck the idea of combining p-aminophenyl stibnic acid with urea, to produce what he described in 1920 as "Urea Stibamine". In October 1922, he published in the Indian Journal of Medical Research regarding eight cases of kala-azar successfully treated with urea stibamine. He also mentioned in this paper on his findings on the toxicity of the drug.

After Brahmachari had satisfied himself by preliminary trials that urea stibamine could be used as an ideal drug he supplied this compound to others experienced in the treatment of kala-azar. Major Shortt, I.M.S., special kala-azar officer of Pasteur Institute, Shillong, and Dr. R. Sen described their experiences on the therapy of this drug in Indian Medical Gazette in July 1923. They treated 23 kala-azar cases with urea stibamine with encouraging results. In all the cases, symptoms of the disease disappeared rapidly and no symptom of intolerance was observed. Brahmachari also published in the Indian Journal of Medical Research, April 1924, an account of nine cases of kala-azar resistant to antimony tartrates cured with urea stibamine.

The efficacy of urea stibamine was thus established. It was at Brahmachari's suggestion to the Director, School of Tropical Medicine, Calcutta that Von Hayden's organic antimonials were introduced at the Calcutta School of Tropical Medicine and stibosan was the first such compound tested by Napier in 1923. It was claimed in certain cases that neostibosan was superior to urea stibamine. However observations by the Assam Government did not confirm

* Department of Immunology, Indian Institute of Chemical Biology, Calcutta-700 032.

this belief as narrated in the Annual Public Health Reports of the province of Assam. The report stated that most satisfactory results were obtained during intensive treatment with urea stibamine.

Shortt, the Director, kala-azar Commission (1932) stated : "We found urea stibamine an eminently safe and reliable drug. In seven years we treated some thousands of cases of kala-azar and observed thousands more treated in treatment centres. The acute fulminating type characteristic of the peak period of an epidemic readily responds to drug (urea stibamine) treatment. With cessation of fever, diminution in size of the spleen and return to normal condition of health was observed. Since 1923 when reliable figures for the disease became available by the end of the year under report, no less than 328591 patients were brought under control. It is no exaggeration to say that approximately 3.25 lacs of valuable lives have been saved in the province."

With the dramatic decline in the incidence of kala-azar after World War II as a bonus to the incidental destruction of *Phlebotomus argentipes*, the common vector of *Leishmania donovani* in India by DDT used to control malaria, and the death of Sir Upendranath Brahmachari on February 6, 1946, the success that had followed the massive use of urea stibamine became overshadowed by doubts about its chemical nature, stability and toxicity. Other antimonials were introduced together with stibamidine (a diamidine first studied in the Liverpool School of Tropical Medicine) which replaced urea stibamine. The manufacture of the drug was undertaken by several drug companies. This resulted in the production of several highly dubious and in some cases, very toxic brews in the Indian market. One must however appreciate that the difference in world-wide research efforts of the 1990s and that of 1920s at the time of discovery of urea stibamine in Calcutta is like that between the exploration of space and the flight at Kitty Hawk in 1903. It will be relevant to quote Wallace Peters from his lecture in 1978 in connection with the Lady U.N. Brahmachari Memorial Oration at the University of Calcutta : "Urea stibamine was a compound that could never have seen the light of the day had it been invented in the past decade. Preclinical toxicity tests carried out prior to the first administration of this new drug in human systems were simple, and of such a nature that the compound would not have been contemplated for clinical testing in our modern age of superconscientiousness and highly sophisticated drug toxicity testing regulations. Nevertheless, urea stibamine, produced by Brahmachari in the Research Institute was administered to hundreds and thousands of sufferers from kala-azar". Prior to the use of antimonials 95% of sufferers had perished : after the invention of urea stibamine the mortality rate was reduced to about 10% in 1925 and by 1936 to just over 7%.

So far as the chemotherapy of kala-azar is concerned, the discovery of urea stibamine by Sir UN Brahmachari is considered as one of the great achievements of the last half century. The discovery of urea stibamine is a monumental work and was amply rewarded by the clinical success. Brahmachari had a special blend of cognitive skill and extraordinary clinical interest. These combined attributes led him to discover "Dermal Leishmanoid"—a skin lesion that develops in certain cases (2 to 3 years) after treatment. Apart from kala-azar research Brahmachari had also contributed in other areas of medical importance such as malaria, filariasis, diabetes, leprosy, meningitis and haematological disorders. But his main claim for recognition from International Science and for remembrance in posterity is based on his life long studies of kala-azar, a dreadful tropical disease responsible for high mortality in some parts of India.

Brahmachari's life was a struggle for the promotion of medical science in the service of mankind. Regarding U. N. Brahmachari it may be truly said :

> "What has passed will never return
> But if it sunk in dazzling flame,
> Flashes of light will still remain".

It is a wonderful thing to carry out a historian's job of the discovery of urea stibamine. Let us pay our tribute to the great soul who remains alive through his scientific progeny.

References

1 U. N. Brahmachari, *Indian J. Med. Res.* **10**, 508, (1922).

2 U. N. Brahmachari, *Indian J. Med. Res.* **10**, 492, (1922).

3 U. N. Brahmachari, Indian Med. Gazette April, 125, (1922).

4 U. N. Brahmachari, (1936) General Presidential Address, Proceedings of 23rd Indian Science Congress, Indore 1.

5 U. N. Brahmachari, (1941) J. Trop. Med. & Hyg. June 3, 1.

6 W. Peter, *Indian J. Med. Res.* **73**, 1, (1981).